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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/847,945	05/02/2001	Neil P. Desai	420042000127	6174

25226 7590 04/12/2006

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EXAMINER	
GOLLAMUDI, SHARMILA S	
ART UNIT	**PAPER NUMBER**
1616	

DATE MAILED: 04/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/847,945	DESAI ET AL.	
	Examiner	Art Unit	
	Sharmila S. Gollamudi	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-17,29 and 31-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-17,29 and 31-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt of Amendments and Remarks filed 1/23/06 is acknowledged. Claims **1, 3-17, 29, 31-55** are pending in this application.

Claim Rejections - 35 USC § 112

The rejection of claims 1, 3-18, and 20-30 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of applicant's arguments which are found to be persuasive.

Claim Rejections - 35 USC § 102

The rejection of claims 18, 20-28, and 30 under 35 U.S.C. 102(e) as being anticipated by Desai et al (5,916, 596) is withdrawn in view of the cancellation of the claims.

Double Patenting

The rejection of claims 18, 20-28, and 30 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2, 4-6, 13-14, and 17 of U.S. Patent No. 6749868 is withdrawn in view of the cancellation of the claims.

The rejection of claims 18 and 20-24 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22-25 of U.S. Patent No. 6096331 in view of Westesen et al (6,197,349) is withdrawn in view of the cancellation of the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The rejection of claims 1, 3-17, and 29-30 under 35 U.S.C. 103(a) as being unpatentable over Desai et al (5,916, 596) in view of Kinsella et al (5,616,608) or vice-versa wherein claims 1, 3-18, and 20-30 are rejected over Kinsella et al in view of Desai et al is withdrawn in view applicant's statement under 103(c).

Claims 1, 3-17, 29, 31-33, 39-41, 47-49, and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kunz et al (5,733,925) of Westesen et al (6,197,349).

Kunz et al disclose methods for inhibiting stenosis following vascular trauma or disease, cancer, diseases resulting from hyperactivity or hyperplasia of somatic cells. Example 7 discloses smooth muscle proliferation in the neointima. Kunz teaches direct or targeted delivery of therapeutic agents to vascular smooth muscle cells. See column 1, lines 15-35. Inhibiting stenosis

following angioplasty is contemplated. See column 3, lines 54-62. The dosage forms are preferably in biodegradable microparticulates or nanoparticulates wherein the particles are formed of a polymer-containing matrix that biodegrades. Kunz et al teach conjugating the drug with a binding protein to target the cells and reduce toxicity. Example 7 notes the toxicity of a free drug versus a conjugated drug. See column 14, lines 25-33. Kunz et al disclose that the direct sustained release dosage form-binding protein or peptide conjugations may disrupt binding protein/peptide target cell recognition. Therefore, ligand sandwich attachment techniques are utilized. Such a technique involves the formation of a primary peptide or *protein shell* using a protein that does not bind to the target cell population. The binding protein/peptide is then bound to the primary peptide or protein shell to provide a particulate with functional binding protein/peptide. For example, the poly-lactic/glycolic acid particulates are reacted with avidin or streptavidin to form *protein-coated particulates*. Additionally, the binding protein/peptide may be partially entrapped in the particulate polymeric matrix upon formation of the particulate. See column 25, line 20 to column 26, line 40. Therapeutic agents such as taxol or analogs are preferred therapeutic agents that are designed to target the cell activity without killing the cell. Taxol is taken into the cell and stabilizes the cell from further dividing. See column 4, lines 40-45 and column 13, lines 24-27. Examples of dosages include .01 to 10 mg/kg per day. For prevention of restenosis following angioplasty or an intervention that contributes to the acute proliferation of smooth muscle cells, a pre-loading dose is given prior to or at the time of intervention with smaller chronic doses given two or three weeks after intervention. For example, a single dose may be administered about 24 hours prior to intervention, while multiple preloading doses may be administered daily for several days prior to intervention. See column

29, lines 10-15. Delivery of the active agents may be intravenous, intra-arterial (stents), or local delivery. See column 30, lines 56-65 and examples for stent deployment.

Kunz et al do not specify the drug form, i.e. instant amorphous form.

Westesen et al teach nanoparticles containing various poorly water-soluble drugs. See abstract. Westesen teaches the use of an amorphous form of the drug to provide for better solubility and bioavailability of poorly water-soluble drugs than utilizing a crystalline form. See column 5, lines 45-56. Generally amorphous forms of a substance exhibit a higher solubility and a faster dissolution than the crystals forms since they do not require lattice energy.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize an amorphous drug form in Kunz et al's nanoparticles. One would have been motivated to do so since Westesen teaches the use of an amorphous form for better solubility and bioavailability of poorly water-soluble drugs. Moreover, one would reasonably expect success by applying Westesen's teachings to Kunz since both are directed to poorly water-insoluble drugs.

Response to Arguments

Applicant argues that in instant invention, the amorphous drug is in the nanoparticulate form, which is coated with a protein. Applicant argues that in the instant invention the nanoparticles do not use a polymeric core material to form the matrix of the nanoparticles. Applicant argues that Kunz does not teach or suggest such methods. According to applicant, Kunz discloses use of drug conjugated to a vascular smooth muscle cell binding protein and the nanoparticulate forms contain a polymeric matrix.

Applicant's arguments filed 1/23/06 have been fully considered but they are not persuasive for the following reasons. The examiner points out that claims are given the broadest

reasonable interpretation and in instant case, the claim language does not exclude the polymer of Kunz. The claims do not specify the nature of the coating and the thickness of the coating. On column 9, lines 37-43, Kunz defines "coupled" to mean covalent and non-covalent chemical association (i.e., hydrophobic as through van der Waals forces or charge-charge interactions) of the matrix or vascular smooth muscle binding protein with the therapeutic agent. Kunz further states on column 26, line 37 et seq., that the carboxylic acid functional groups are coupled to binding protein or peptide. These statements clearly imply that the protein taught by Kunz is around the therapeutic agent, i.e. meaning that the therapeutic agent is coated. Furthermore, as already pointed out in the previous Office Actions, the polymeric particles in Kunz can also coated with avidin, which is a protein. Thus, it is the examiner's position that Kunz's meets the instant required claims limitations.

Applicant's arguments with regard to Westesen are substantially similar to those presented on 6/3/05 and are not found to be persuasive. In essence, the examiner points out that Western is combined for its teachings of use of amorphous form of the drug and for its teachings of improved bioavailability of the drug and not for its teachings of the method of formation of the particles. Applicant argues that Westesen would be incompatible with the function of the protein since supercooled substances have very different characteristics; however applicant does not provide any support for such an assertion. The examiner further points out that on column 5, wherein Westesen clearly states:

> Apart from reduction of particle size and improvement of wettability, the peroral bioavailability of a poorly water-soluble drug can be enhanced if the drug is not present in a crystalline but in an amorphous physical state. In general, amorphous forms of a substance exhibit a higher solubility and a faster dissolution than their crystal forms since the dissolution of amorphous substances does not require lattice energy. It is

known, for example, that the antibiotic agent novobiocin can only be absorbed from the intestinum after administration of the amorphous substance which has a solubility ten times higher than the crystalline agent (Mullins J. D., Macek T. J., J. Am. Pharm. Assoc., Sci. Ed. 49 (1960) 245).

Thus, it clear that Westesen's teachings regarding amorphous drugs it what is known in the prior art and the characteristics/properties of the amorphous drug in *general*.

Claims 38, 46 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kunz et al (5,733,925) in view of Westesen et al (6,197,349), further in view of Mitragotri (5,814,599) or JP 05294839.

The teachings of Kunz and Westesen have been discussed above.

The references do not teach the use of albumin as the polymeric material making the nanospheres.

Mitragotri while disclosing drug delivery devices teaches the equivalency between particles made of polylactic acid, polyglycolic acid, and albumin. The particle sizes include 0.001 microns. See column 5, lines 5-16.

JP similarly teaches the equivalency between microspheres of polylactic acid, copolymer of lactic/glycolic acid and albumin. See abstract.

It would have been obvious for one of ordinary skill in the art at the time the invention was made to combine the teaching of the above references and utilize albumin instead of polylactic acid or polylactic/glycolic acid polymers. One would have been motivated to do so with a reasonable expectation of success since Mitragotri and JP both teach the equivalency of these polymers in terms of drug delivery.

Claims 34, 35, 42, 43, 50 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kunz et al (5,733,925) in view of Westesen et al (6,197,349) further in view of Hunter (5,994,341).

The teachings of Kunz and Westesen have been discussed above. Kunz teaches the use of therapeutic agents such as taxol or analogs, specifically paclitaxel, are preferred therapeutic agents that are designed to target the cell activity without killing the cell. Kunz teaches cytoskeletal inhibitors such as taxol act on the microtubule and microfilament networks within the cell. See column 18, lines 64-67.

Neither Kunz nor Westesen teach the specific use of epothilone as the antiproliferative agent.

Hunter teaches both epothilone and paclitaxel disrupt microtubule function. See column 15, lines 48-55.

It would have been obvious for one of ordinary skill in the art at the time the invention was made to combine the teaching of the above references and utilize the instantly claimed drug. One would have been motivated to do so with a reasonable expectation of success since Hunter teaches that both paclitaxel and epothilone are both agents which disrupt microtubule function. The selection of a specific drug is considered prima facie obvious to a skilled artisan in the art.

Claims 36-37, 44-45, 52-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kunz et al (5,733,925) in view of Westesen et al (6,197,349) further in view of Marx (Circ. Res. Vol. 76, pp. 412-417, 1995).

The teachings of Kunz and Westesen have been discussed above. Kunz teaches the use of smooth muscle inhibitors for the treatment of restenosis.

Neither Kunz nor Westesen teach the specific use of rapamycin as the antiproliferative agent.

Marx teaches rapamycin is an inhibitor of smooth muscle cells in the abnormal proliferation of restenosis. See abstract.

It would have been obvious for one of ordinary skill in the art at the time the invention was made to combine the teaching of the above references and utilize the instantly claimed drugs. One would have been motivated to do so with a reasonable expectation of success since Marx teaches the rapamycin is a smooth cell inhibitor useful in treating restenosis. The selection of a specific drug is considered prima facie obvious to a skilled artisan in the art.

Conclusion

The reference of Gregory (Transplantation, vol. 59, pp. 655-661, 1995) is cited as art of interest.

All the claims remain are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

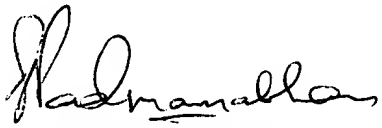
however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharmila S. Gollamudi whose telephone number is 571-272-0614. The examiner can normally be reached on M-F (8:00-5:30), alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 571-272-0887. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sharmila S. Gollamudi
Examiner
Art Unit 1616



SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER